

Biotechnology Licensing  
IP Section Licensing Committee  
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# Background

- 3 areas of biotechnology licensing
  - Pharmaceutical (e.g., polypeptides, proteins antibodies)
  - Agricultural (engineering plants, seeds, for new characteristics)
  - Industrial (enzymes in production processes, cosmetics, food)

# Pharma/Biotech Background

- US Food & Drug Administration [www.fda.gov](http://www.fda.gov)
  - Regulates all aspects of drug development and approval
    - Federal Food, Drug, and Cosmetic Act (Title 21, Chapter 9) (aka FFDCA)
    - Regulations (21 CFR 1 et seq)
    - See the Story Behind the FFDCA (attached)

# How to get a drug approved

- Identify a lead molecule and conduct tests
  - Animal studies
  - Toxicity
  - Pharmacokinetics
- Submit Investigative New Drug Application (IND)
  - FDA has 30 days to approve or hold

# How to get a drug approved

- Phase I
  - Safety and Toxicity
- Phase II
  - Can have multiple Phase II trials
  - Define criteria (endpoint)
  - Efficacy
- Phase III
  - Broad based trial for efficacy and safety
  - Representative population

# How to get a drug approved

- Submit New Drug Application (NDA)
  - Wait for FDA approval letter (or not)
- Launch
- Post-Marketing Studies (aka Phase IV)

# Aspects to Move the Process Along

- “Fast Track” (21 CFR 256)
- Orphan Drug Designation (21 CFR 360bb)
- Pediatric Studies of Drugs (21 CFR 355a)
- Prescription Drug User Fee Act of 1992 (PDUFA) (“pay to play”)

# Drug Price Competition and Patent Term Restoration Act of 1984

- Hatch-Waxman Act
- See, Mossinghoff, *Overview of the Hatch-Waxman Act and its Impact on the Drug Development Process*, Food and Drug Law Journal, Vol. 54, page 187  
[http://www.fdli.org/pubs/Journal%20Online/54\\_2/art2.pdf](http://www.fdli.org/pubs/Journal%20Online/54_2/art2.pdf)

## 2 Components of Hatch-Waxman - Patent Term Restoration

- 35 USC 156, 271, 282
  - Administered by US Patent & Trademark Office
  - Max to 5 years or 14 years total market exclusivity
  - 1 extension per drug
  - “Do the math” 35 USC 156
    - ( $\frac{1}{2}$  IND days + 1 NDA days) – applicant delays = extension term

## 2 Components of Hatch-Waxman - Drug Exclusivity

- Administered by FDA
- 21 USC 321, 331-32, 348, 351-53, 355, 357-60, 372, 374, 376, 381
  - NCE or NME = 5 years
  - Formulation = 3 years
  - Orphan = 7 years

# Hatch-Waxman “Safe Harbor”

- 35 USC 271(e)
- Allows a “safe harbor” from infringement for generic manufacturers to generate data for an Abbreviated New Drug Application (ANDA)
  - Bioequivalence and bioavailability
  - Generic can be approved as of the date of expiry of the pioneer drug
  - Chapter IV

# Hatch-Waxman “Safe Harbor”

- Merck KGaA v. Integra Lifesciences I, Ltd. 03-1237 (2005) <http://laws.findlaw.com/us/000/03-1237.html>
  - The use of patented compounds in preclinical studies is protected under 37 USC 271(e)(1) as long as there is a reasonable basis to believe that the compound tested could be the subject of an FDA submission and the experiments will produce the types of information relevant to a new drug application.
- Open Question: When is a drug IN the “safe harbor”?

# ***MedImmune, Inc. v. Genentech, Inc., No. 05-608 (2007)***

<http://laws.findlaw.com/us/000/05-608.html>

- Not biotech specific
- Cabilly
- MedImmune was not required, insofar as Article III is concerned, to break or terminate its 1997 license agreement before seeking a declaratory judgment in federal court that the underlying patent was invalid, unenforceable, or not infringed.

# Dealing with *MedImmune*

- Penalties for filing suit
  - Automatic termination
  - Contractually limit damage award
  - Increase fees
- “Don’t bother to license anything anymore,” sayeth an anonymous biotech lawyer colleague of Joyce

# Pharma/Biotech Licensing Strategies

- Platform – “Seed the world”
  - Non-exclusive License
    - PDL’s “Humanization”
    - Genentech’s “Cabilly”
  - Field Licenses
- NCE or NME
  - Generally Exclusive
  - Field Licenses
    - Geography
    - Indication
    - Market Segment

# Pharma/Biotech Harsh Realities

- 1 in 10 INDs results in an approved drug
- Time to approval is 8-10 + years
- Cost for each drug development is \$10 Million +++
- Term for exclusivity may be shortened by Generics
- Potential changes to pioneer drug landscape
- Impact of “biogenerics” legislation

# General Issues in a Pharma/Biotech License

- Due Diligence
- Upfront Payment & Milestones
- R&D Support
- Clinical Support
- Royalties
- Marketing and Promotions Rights
- Patent stuff
- Litigation
  - Clinical liability
  - Infringement/Invalidity
  - Product Liability

# Due Diligence and Valuation

- Is patent in force? 😊
- Confidentiality – Community of Interest
- Infringement/Validity Assessment
- Trade secrets/know-how/improvements included?
- International patent status
- US and international regulatory status
- Review of data: CMC, pre-clinical, clinical, AEs
- Hart-Scott-Rodino required? [www.ftc.gov/bc/hsr/](http://www.ftc.gov/bc/hsr/)
- **For All Answers see: Bjorkman, *Due Diligence from the Perspectives of the Licensor and Licensee*, May 15, 2009 (attached)**

# General Terms of a Pharma/Biotech License – Upfront and Milestone Payments

- IND submission
- Phase I start
- Phase II start
- Phase III start
- NDA submission
- USFDA approval
- ROW approval
- Indication Approval
- Follow On Indication Approval
- Pediatric Drug Approval
- **Upfront** may be cash, reimbursement for certain incurred expenses, equity, debt

# Who pays?

- R&D and clinical costs are expensive
- Big Pharma has expertise in moving drugs through the clinic to approval
- Biotech is innovative but cannot afford large clinical trials

# Who Pays – Possible Solutions

- Big Pharma pays for clinical trials in return for accommodation in royalties
- Big Pharma/Biotech split costs and biotech gets greater share of royalties
  - Biotech does some validation or other work as in kind contribution

# Managing the Pre-Clinical/Clinical /Marketing/Launch Process

- Form a Steering Committee with both parties to manage the process
  - Membership changes as drug progresses through process
  - Biotech gains clinical trial/regulatory experience
  - Big Pharma has access to scientific expertise from Biotech developers
  - Good “relationship” tool

# Royalties – things to keep in mind

- Royalty Stacking
  - Cabilly (Genentech) antibody production
  - Queen (Protein Design Labs) “antibody humanization”
  - Fc Engineered Antibodies (SB2, Xencor, Genentech, PDL)
  - T7 Technology (Brookhaven Labs) protein production
  - Vector Components
    - e.g., cmv promoter (University of Iowa)
- Use of Research Tools (e.g., assays, use of antigens)
  - “Reach through claims”
  - see footnote 7, Merck v. Integra)

# Strategy for Royalties cont'd

- Build in anticipated royalty stack for final royalty
- Get royalty set-off (reduction) for these payments
- Potential application of 271(e)(1) “safe harbor” to avoid royalty payments on “old patents”

# Strategy for Royalties cont'd

- Royalties increase the further a drug is in development
- Usual Value Inflection Points
  - IND approved
  - Successful completion of Phase I study (especially if there is hint of efficacy)
  - Successful completion of Phase II study
  - Successful completion of Phase III study

# Royalties cont'd

**ALWAYS** provide an audit provision and use it!

# Marketing and Promotion Rights

- If Biotechs share in costs, they get increased royalties
  - Some cost and risk set off for Big Pharma
  - Not all biotechs are competent to market and co-promote
- Who decides indications to get approved & markets?
- Define the message and strategy
  - Watch for promotion of unapproved uses
  - Division of Drug Marketing, Advertising & Communications (DDMAC)
    - <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/DrugMarketingAdvertisingandCommunicationsResearch/default.htm>

# Patent Stuff

- Control of patent WW filing & prosecution
  - Licensors should try to keep this responsibility to ensure appropriate patent coverage
  - Who decides where to file (and who pays)
  - How to deal with the costs?
    - If control, pay all
    - Negotiate some reimbursement of expenses
  - Control of patent term extension strategy

# Clinical Trial Litigation

- Informed Consent: Important to be clear about the risks and adverse events
- Generally if negligence is due to site/doctor, then site pays
- Injury due to the drug itself is paid by Sponsor
  - negotiation point between licensor and licensee
- Some institutions require Sponsor pay regardless of who is negligent (e.g. Harvard)
- Clinical Trial insurance is critical – starts at \$5 Million for Phase I and increases
  - Read the fine print

# IP Litigation

- Invalidity – Third Party Sues
  - Negotiation Point: Who controls (and pays for) litigation?
    - If it is other party, at least get a right to retain counsel and have them be a party to any protective order
- Infringement by Third Party
  - Negotiation Point: Who controls (and pays for) and reaps the potential reward?
    - Ditto on bullet above

# IP Litigation cont'd

- Infringement of Research Tool of Third Party
  - E.g. Cabilly license from Genentech
  - Strategy – litigate or settle – who makes decision?
- Chapter IV under Hatch-Waxman
  - Generic sues to invalidate patent before expiration
    - Who controls (and pays for) litigation
    - Patent holder has 60 days after notice by FDA to file suit

# Product Liability Litigation

- Liability may lie with manufacturer, patent holder, licensee, sublicensee, marketer, promoter, doctor (“learned intermediary”)
- Philosophy to sue everyone and sort it out later
- *Conte v. Wyeth, Inc. et al* (2008)
  - See <http://www.crowell.com/documents/Direct-Liability-for-Pioneer-Drug-Manufacturers-in-Suits-Involving-Generic-Products.pdf>
    - Wyeth found liable when patient used a non-Wyeth generic version of a Wyeth drug!

# The End of a Beautiful Relationship?

- When Licensee terminates early
  - Who gets the rights – patents, data, supply?
  - Is there reimbursement for costs?
- When Licensee or Licensor is acquired
  - Automatic right of termination
  - Right of termination with good cause
- Bankruptcy
  - Who knows?

# Miscellaneous

- Consider obtaining lesser royalties for sales in non-patent countries for a defined term (e.g., 10 years)
- Consider obtaining lesser royalties if no patent is obtained for a defined term
- Deal with in-country competition (e.g. non-infringing competitive products)
- Don't forget off-sets for additional required patent licenses (e.g., Cabilly)

# Blogs/Websites

- BioSpace Deals & Dollars [newsletters@biospace.rsys1.com](mailto:newsletters@biospace.rsys1.com)
- Ken Adams Contract Drafting [kadams@adamsdrafting.com](mailto:kadams@adamsdrafting.com)
- FDA Law Blog [fdablog@hpm.com](http://fdablog@hpm.com)
- Orange Book Blog <http://www.orangebookblog.com/>
- Patent Term Extension (Restoration) under 35 USC 156 Decisions <http://www.uspto.gov/web/offices/com/sol/foia/comm/pte/pte.htm>
- Patent Docs (Court Report) <http://www.patentdocs.org>
- Pending biologics legislation in Canada <http://www.hc-sc.gc.ca/dhp-mpps/consultation/biolog/2009-03-seb-pbu-notice-avis-eng.php>
- Biotechnology Industry Organization (BIO) <http://www.bio.org/>
- Pharmaceutical Research and Manufacturers of America (PhRMA) <http://www.phrma.org/>
- Generic Pharmaceutical Association <http://www.gphaonline.org/>
- IguanaBio (gossip) <http://www.iguanabio.com/>
- Pharma Babble (Biomedical BD and investment) <http://www.pharmababble.com/>

# Agricultural Biotech - Background

- Environmental Protection Agency
  - Administers regulations for approval of new pesticides
    - No Hatch-Waxman
    - “me-toos” can obtain approval by negotiating payment for pioneer product data
    - Need trials to determine toxicity and impact to environment
    - Registration of product can be re-evaluated at any time
      - Organo-phosphates

# Agricultural Biotech - Background

- US FDA
  - Administers regulations relating to human food products and certain animal feeds
    - US Department of Agriculture also involved
  - “Delaney Clause” (1938)
    - *The Jungle* (Upton Sinclair)
    - No food additive was safe (approvable) if found to cause cancer in man or experimental animals
      - Pesticide residue in food
      - Is it “fair” today?

# Agricultural Biotech - Background

- Genetically Modified (GM) Foods or Functional Foods
  - Food products that are modified to provide enhanced properties
    - “golden rice” – enhanced levels of beta carotene
    - Pesticide resistance (e.g. RoundUp® Ready corn)
    - bt milk products
- Area is controversial and in flux

# Licensing Issues

- GM plants and seeds
  - Most licensing is from Academia to Business
  - Not many start up biotech ag companies
    - Technology to generate chemicals/drugs via engineered plants
      - See <http://www.planetbiotechnology.com/>
    - “Natural products” use in processes
      - <http://www.agilesci.com/index.html>

# Industrial Applications

- Cosmetics and Nutraceuticals
  - US FDA administers products and additives
    - Must be “GRAS” – generally recognized as safe
    - New additives must undergo testing and USFDA approval before use
    - Drug claims – must undergo clinical trial
      - “eliminates acne”
      - “cures cancer”
- US FDA is considering regulating nutraceuticals  
<http://www.fimdefelice.org/clippings/clip.fdaweek.html>

# Industrial Enzymes

- Industry slow to adopt biotech solutions
- Enzymes are exquisitely specific
  - Engineered to replace production steps
  - Driven by environmental regulation and being “green”
    - E.g., eliminates use of chlorides in process
  - Richards, J.J., Reed, C.S., and Melander, C. Effects of N-Pyrrole Substitution on the Anti-Biofilm Activities of Oroidin Derivatives Against *Acinetobacter baumannii*. *Bioorganic & Medicinal Chemistry Letters*, **2008**, 18 (15), 4325-4327.
- Royalties are very low – make \$\$\$ on volume